REMARKS

Claims 1-62 are currently pending in this application. Claims 13-29, 31-44, 47-52, 58, 61, and 62 are withdrawn from consideration. Claim 54 is rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. Claims 1-12, 30, 45, 46, 53-57, 59, and 60 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. Claims 1-12, 30, 45, 46, 53-57, 59, and 60 are provisionally rejected for obviousness-type double patenting over claims 1-14 and 35-49 of co-pending U.S. Serial No. 10/358,664. Finally, claims 1-12, 30, 45, 46, 53-57, 59, and 60 are rejected for obviousness-type double patenting over claims 1-15 of U.S. Patent No. 6,660,487. The Office also objects to the title and the specification. By this reply, Applicant amends the title and specification, amends claim 54, and addresses each of the objections and rejections below.

Support for the Amendment

The title of the application has been amended, as requested by the Office, to better describe the invention to which the claims are directed. Applicant has also amended the specification to add sequence identifiers to the sequences listed on page 28.

Support for the amendment to claim 54 is found in the specification at, e.g., page 10, lines 1-22. No new matter is added by the amendment.

Rejection under 35 U.S.C. § 112, second paragraph

The Office rejects claim 54 under 35 U.S.C. § 112, second paragraph, for indefiniteness, stating there is insufficient antecedent basis for the limitation "'blood cells'...since the base claims do not recite[] blood cells" (Office Action, p. 3). Applicant has amended present claim 54 to replace the term "blood cells" with the term "cell populations," which has antecedent basis in claim 53, from which claim 54 depends. This rejection can be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 1-12, 30, 45, 46, 53-57, 59, and 60 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Office states:

> The specification only discloses limited data obtained on NOD female mice

> wherein treatment with live splenocytes and CFA prolong survival of syngeneic islet graft and...[restores] normoglycemia (see examples 1-4 and Table 1 and 2 in particular)...[S]ince there is no animal model studies and data in the specification to show the effect[] of the claimed method for increasing or maintaining the number of any functional cells of any predetermined type of any organ or any tissue comprising administration to the subject a composition of enriched pluripotent cells that express Hox 11 gene alone or in combination with administering TNF-alpha or TNF-alpha agonist or TNF-alpha inducing substances, [it] is unpredictable how one skilled in the art can practice the invention without an undue amount of experimentation.

(Office Action, pp. 3-5.) Applicant respectfully traverses this rejection.

The M.P.E.P. § 2164.01(b) states that "[a]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. § 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)." Applicant has plainly met this standard.

Present independent claim 1 is directed to a method for increasing or maintaining the number of functional cells of a predetermined type in an organ or tissue of a mammal (e.g., a human), in which the organ or tissue is injured, damaged, or deficient in the functional cells, by administering to the mammal a composition enriched in pluripotent cells that express the *Hox11* gene. The invention featured in present claims 1-12, 30, 45, 46, 53-57, 59, and 60 is based, at least in part, on Applicant's discovery that *Hox11*-expressing cells, which are present in the capsule of normal human spleen, represent a previously unknown reservoir of pluripotent cells not found in other human hematopoietic tissues, such as bone marrow and thymus, or in other examined peripheral organs; *Hox11*-expressing cells play a role in the genesis of the spleen and other peripheral tissues. Applicant recognized that the administration of *Hox11*-expressing cells to a mammal can restore or maintain organs or tissues in a mammal by replacing lost or damaged functional cells, such as, e.g., beta-islet cells, as a result of the differentiation of the *Hox11*-expressing cells into the lost or damaged functional cells.

Applicant's discovery is described in enabling detail in the present specification, which teaches that "[t]he invention relates to repairing and regenerating damaged tissue in a mammal (e.g., a human patient). Such damage may result from an existing autoimmune disease, or may

be the result of a non-autoimmune insult" (Specification, p. 1, lines 12-14). The specification further teaches that:

> the invention employ[s] pluripotent cells that express Hox 11, isolated from a normal donor (e.g., from the bone marrow, the spleen, or the peripheral blood, preferably from the spleen). Typically, this cell expresses, to a detectable degree, $CD90^+$, $CD44^+$, or $CD29^+$, but does not express appreciable amounts of CD45 or CD34. **This normal donor cell is administered to a person, preferably intravenously or intraperitoneally, to allow for rapid transport to the site of inflammation, injury, or disease. Desirably, this cell is administered to a person with active autoimmunity. Alternatively, the cell may be administered to a person without autoimmunity or to a person with quiescent autoimmunity.** The absence of active autoimmunity in a person (host) may require pretreatment of the host to initiate an inflammatory response or injury at the regenerative site. In addition, pretreatment of the donor cell may also be required. The host may be treated with TNF-α, IFN-γ, IL-2, VEGF, FGF, or IGF-1 to prepare the blood vessel endothelium for optimal interactions with the mobilized Hox 11-expressing cell. Additionally, the pathway of VEGF-stimulated expression on endothelial cells can be enhanced with a selective inhibitor of PI-3'-kinase. Alternatively, the host can be pretreated with platelet-derived growth factor derived from mural cells (e.g., from the neural crest or epicardium) for optimal interactions with the mobilized mesodermal cell. Additionally, the mesodermal cell can be pretreated to optimize adherence to the endothelium. **This type of therapy is envisioned to be beneficial for the regeneration of diverse organs or organelles, including islets of Langerhans, liver, pancreas, spleen, and bone.**

(Specification, p. 50, line 6, through page 51, line 2; emphasis added.)

The present specification exemplifies the invention by reference to a preferred embodiment, which examines the restoration of beta-islet cells following the administration of *Hox11*-expressing splenocytes using an NOD mouse model. The NOD mouse model is an accepted animal model of type 1 (autoimmune) diabetes mellitus, Sjögren's syndrome, and lupus in humans, and is a fitting model for demonstrating the application of Applicant's invention because NOD mice are deficient in several different types of functional cells, many of which are derived from the pluripotent *Hox11*-expressing cells, including, e.g., beta islet cells of the pancreas, salivary gland cells, and cells of cochlear tissues of the inner ear. In particular, Examples 1 and 2 of the specification reveal that the administration of live donor splenocytes (i.e., *Hox11*-expressing cells) to diabetic NOD mice resulted in the restoration of normoglycemia

in 6 out of 9 mice in a first study (Example 1) and in 11 out of 12 mice in a second study (Example 2)(Specification, pp. 29-33). The specification further teaches that "the pancreata of NOD mice that received live splenocytes exhibited the reappearance of pancreatic islets without invasive insulitis and with minimal or no peri-insulitis" (Specification, p. 33, lines 6-8).

The specification provides further evidence in Example 3 that the administered *Hox11*-expressing cells persist in the host mammal after administration, teaching that "NOD mice treated with live splenocytes...exhibited a persistent low level of blood chimerism with semiallogeneic cells that was achieved without continuous immunosuppression or lethal preconditioning" (such as whole-body irradiation)(Specification, p. 34, line 23, through page 35, line 2). Finally, Example 4 of the present specification confirms that it is the administered *Hox11*-expressing cells that contribute to islet regeneration, teaching that

> Quantitative analysis revealed that 29% to 79% of islet cells in...five animals [administered *Hox11*-expressing splenocytes] were of donor origin. No islets solely of host origin were detected, consistent with the fact that the pancreas of NOD females before treatment lacks detectable islets as well as remaining clusters of insulitis.

(Specification, p. 36, line 23, through page 37, line 2.) Thus, the present specification clearly teaches, and provides experimental evidence that confirms, that the administration of *Hox11*-expressing cells to a mammal having an injured, damaged, or deficient organ or tissue, in this case a damaged pancreas, increases the number of functional cells in the mammal, here beta islet cells of the pancreas, reverses invasive insulitis, and restores normoglycemia. Accordingly, Applicant submits that present claims 1-12, 30, 45, 46, 53-57, 59, and 60 plainly satisfy the enablement requirement of 35 U.S.C. § 112, because Applicant's specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to their entire scope (M.P.E.P. § 2164.01(b)).

In addition, as further evidence that the full scope of present claims 1-12, 30, 45, 46, 53-57, 59, and 60 is enabled, Applicant directs the Office to the enclosed Declaration of the inventor, Dr. Denise Faustman, who attests that her data further confirm that *Hox11*-expressing splenocytes can be administered to increase or maintain the number of functional cells of a predetermined type in the organ or tissue of a mammal that is injured, damaged, or deficient in

the functional cells (see ¶ 5 of the Declaration). Dr. Faustman states that, in addition to the regeneration of pancreatic beta islet cells, the method of present claims 1-12, 30, 45, 46, 53-57, 59, and 60 have been successfully demonstrated in an NOD mouse model, which is an accepted animal model of type I diabetes, Sjögren's syndrome, and lupus in humans (¶ 6 of the Declaration), to treat salivary gland defects similar to those observed in human patients having Sjogren's syndrome by regenerating acinar epithelial cells and to regenerate tissues in the inner ear leading to the restoration of hearing (see ¶¶ 7 and 8 of the Declaration). In addition, Dr. Faustman states that her data further confirm that the administration of *Hox11*-expressing cells in combination with TNF-α, a TNF-α inducing substance, or a TNF-α agonist, promotes the regrowth of damaged glands and tissues and, in some instances, stimulates the endogenous regeneration of damaged adult tissues (see ¶ 5 of the Declaration).

In particular, Dr. Faustman states that researchers working under her direction have shown that *Hox11*-expressing cells, when administered to NOD mice exhibiting histopathological and functional changes in their salivary glands that mimic the changes observed in patients with Sjögren's syndrome, regenerate salivary gland tissue and restore saliva production (¶ 7 of the Declaration). As described in ¶ 7 of the Declaration, NOD mice exhibiting symptoms characteristic of advanced Sjögren's syndrome (greater than 50% loss of salivary flow) were treated with an injection of male donor *Hox11*-expressing splenocytes bi-weekly for 40 days and exhibited a gradual improvement in salivary flow rate (SFR) 120 days following treatment (Fig.1A of the Declaration). By 160 days, the SFR of the treated NOD mice was comparable to that of age-matched normal C57BL/6 mice ($p=0.6434$). The treated NOD mice were also protected from diabetes ($p=0.0002$; Fig.1B). In contrast, the SFR of untreated NOD continued to deteriorate over time, and all of them died of severe hyperglycemia within 140 days from the start of therapy.

In addition, Dr. Faustman further states that an examination of the salivary tissues of the female NOD mice treated with the *Hox11*-expressing splenocytes, using immunohistochemical staining (IHC) and fluorescence *in situ* hybridization (FISH) to detect the Y chromosome and specific markers for salivary or pancreatic cells, revealed the presence of a small number of Y-positive salivary epithelial cells (see ¶ 7 and Figs. 2A-D of the Declaration) and a few pancreatic

beta cells; these cells were not observed in the untreated NOD or normal C57BL/6 mice (¶ 7 of the Declaration). Thus, Dr. Faustman's data confirm that the donor *Hox11*-expressing splenocytes colonized the salivary gland, differentiated into salivary epithelial cells, and restored salivary gland tissue and function.

Applicant next directs the Examiner to ¶ 8 of the Declaration, which states that *Hox11*-expressing cells also demonstrate the ability to replace and/or regenerate adult inner ear tissues of the cochlea, thereby restoring hearing and inner ear anatomy to varying degrees, as determined functionally and histologically. NOD mice, in addition to having deficiencies in their pancreas and salivary glands, as is discussed above, exhibit structural and functional deficiencies in inner ear structures that result in complete hearing loss at early stages of post-natal life. Because cranial nerve dysfunction, especially sensorineural hearing deficits, has been frequently documented in humans with Sjögren's syndrome and in some studies in diabetic patients, the NOD mouse model, which exhibits sensorineural hearing deficiencies similar to those observed in humans, provides a useful model for studying therapeutic regimens for treating these deficiencies in humans.

As is discussed in ¶ 8 of the Declaration, Dr. Faustman attests that *Hox11*-expressing splenocytes from normal adult mice administered to NOD mice engraft within inner ear structures (e.g., the spiral ligament and organ of Corti) and stably restore long-term hearing in deaf NOD mice. Two of eight treated NOD mice, when evaluated electrophysiologically by measuring auditory brainstem responses (ABR) and histologically, showed significant recovery in hearing (e.g., a return of most low and mid-frequency hearing); the remaining six NOD mice showed slight increases in hearing, as measured by lower thresholds in the ABR test (See Fig. 3 of the Declaration). As shown in Fig. 4 of the Declaration, the two NOD mice whose functional hearing was significantly improved appeared to have a normal spiral ligament with a full, or nearly full, population of cells in the lower third turn (Figs. 4A and 4C) and lower second turn (Figs. 4B and 4D) of the cochlea. Also, the organ of Corti was restored in both treated NOD mice based on the presence of a full population of cells, including hair cells, and the apparent restored development of the tunnel of Corti in the lower second and third turns (see Figs. 4A-D). In contrast, one of the six treated NOD mice that did not exhibit a significant improvement in

hearing, when examined histologically, continued to show severe atrophy of cells in the spiral ligament of the lower third turn and lower second turn, which is depicted by a depopulation of cells in the area that corresponds to the spiral ligament in Figs. 4E-F. This mouse did have some apparent improvement in the organ of Corti, in particular, the lower second turn contained a few cells, e.g., inner and outer hair cells (see Fig. 4F), when compared to an untreated NOD mouse, but continued to have the persistent poor development of the tunnel of Corti (see Fig. 4E), which is similar to that observed in a normal C57BL/6 control mouse (see Fig. 4G). Thus, Dr. Faustman's further data demonstrate that *Hox11*-expressing cells, when administered according to the methods of present claims 1-12, 30, 45, 46, 53-57, 59, and 60, exhibit the ability to engraft within tissues of the inner ear, to regenerate injured, damaged, or deficient functional inner ear cells, and to fully restore hearing in 25% of treated NOD mice compared to age matched control mice. In addition, restored partial hearing recovery was observed in another 25% of treated NOD mice.

Accordingly, Dr. Faustman's data further confirm the ability of *Hox11*-expressing cells to increase or maintain the number of functional cells of a predetermined type in an injured, damaged, or deficient organ or tissue of a mammal by engrafting in the organ or tissue and differentiating into functional cells or promoting the increase or maintenance of endogenous functional cells in the organ or tissue. Applicant submits that the data presented in the Declaration confirm that the methods taught in the specification are fully enabled. Thus, for the reasons discussed above, the method of present claims 1-12, 30, 45, 46, 53-57, 59, and 60 can be performed without undue experimentation. For this reason, the rejection of present claims 1-12, 30, 45, 46, 53-57, 59, and 60 under 35 U.S.C. § 112, first paragraph, for lack of enablement should be withdrawn.

Applicant has Satisfied the Standard for Enablement

Applicant has provided more than enough evidence to satisfy the burden of proof set forth in *In re Brana* (51 F.3d 1560, 1567, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995)) for demonstrating enablement, as is discussed below.

In *Brana*, the court cautioned against confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption," citing *Scott v. Finney*, 34 F3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994). The rejection before the court for review in *Brana* was for lack of enablement under the first paragraph of 35 U.S.C. § 112 (although the court discussed the issues raised in the appeal in the context of both enablement and the utility requirement of 35 U.S.C. § 101):

> On the basis of animal studies, and controlled testing in a limited number of humans (referred to as Phase I testing), the Food and Drug Administration may authorize Phase II clinical studies. [ ] Authorization for a Phase II study means that the drug may be administered to a larger number of humans, but still under strictly supervised conditions. The purpose of the Phase II study is to determine primarily the safety of the drug when administered to a larger human population, as well as its potential efficacy under different dosage regimes. [ ]
>
> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. [ ] Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer. *Brana*, 51 F3d at 1568, 34 USPQ2d at 1442-43 (citations omitted).

While the claims involved in *Brana* were directed to chemical compounds taught to be useful in treating cancer, Applicants submit that these principles can be applied to the present claims directed to a method for increasing or maintaining the number of functional cells of a predetermined type in an organ or tissue of a mammal (e.g., a human), in which the organ or tissue is injured, damaged, or deficient in the functional cells, by administering to the mammal a composition enriched in pluripotent cells that express the *Hox11* gene. Thus, as in *Brana*, where the Court held that the applicants' declaratory evidence showing antitumor activity in an *in vivo* mouse model was sufficient to satisfy the utility and enablement requirements of 35 U.S.C. § 112, first paragraph, Applicants submit that the case law compels the Examiner to conclude that

Applicants' declaratory evidence, which unequivocally demonstrates that the administration of a composition enriched in pluripotent cells that express the *Hox11* gene increases or maintains the number of functional cells of a predetermined type in an organ or tissue of a mammal (e.g., a human) in which the organ or tissue is injured, damaged, or deficient in the functional cells, should also be deemed sufficient evidence demonstrating that the method of present claims 1-12, 30, 45, 46, 53-57, 59, and 60 satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. For this reason as well, the Examiner's rejection of claims 1-12, 30, 45, 46, 53-57, 59, and 60 for lack of enablement should be withdrawn.

Obviousness-Type Double-Patenting Rejection

Claims 1-12, 30, 45, 46, 53-57, 59, and 60 are provisionally rejected for obviousness-type double patenting over claims 1-14 and 35-49 of co-pending U.S. Serial No. 10/358,664 and claims 1-12, 30, 45, 46, 53-57, 59, and 60 are rejected for obviousness-type double patenting over claims 1-15 of U.S. Patent No. 6,660,487. When the pending claims are found to be otherwise allowable except for these grounds of rejection, Applicants will address these rejections, including consideration of whether to file a terminal disclaimer.

CONCLUSION

In view of the above remarks, Applicant respectfully submits that the claims are in condition for allowance, and such action is respectfully requested.

Enclosed is a Petition to extend the period for replying to the Office Action for three months, to and including September 12, 2007, and a check for the fee required under 37 C.F.R. § 1.17(a).

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

TODD ARMSTRONG, PhD
Reg. No. 54,590

Date: 12 September 2007

For Paul T. Clark
Reg. No. 30,162

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045